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EXAMINER
DAVIS, MINH TAM B

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 05/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/967,305	RICHARDSON ET AL.	
	Examin r	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this c mmunication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-58* is/are pending in the application.

4a) Of the above claim(s) *1-32 and 35-58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election of group XXXXV, claims 33-34, SEQ ID NO:1 or 3 in paper No:11, without traverse is acknowledged.

Accordingly, claims 33-34 are examined in the instant application, wherein claims 33-34 are examined only to the extent of a method for identifying candidate therapeutic agents for the treatment of prostate cancer, comprising determining the level of mRNA of SEQ ID NO:1 or 3, an alpha-methylacyl-CoA racemase, in the presence of a test compound .

OBJECTION

1. Claim 34 is objected to because part of claim 34 is drawn to non-elected invention. Claim 33 is drawn to a method for identifying candidate therapeutic agents for the treatment of prostate cancer, comprising determining the level of mRNA of alpha-methylacyl-CoA racemase, in the presence of a test compound, wherein said racemase encompasses not only the elected splice variant of SEQ ID NO:1 and its open reading frame of SEQ ID NO:3, but also the non-elected SEQ ID Nos :4, 6, 8, 10, which are different splice variants of alpha-methylacyl-CoA racemase, as disclosed on pages 11, p.18, last paragraph, of the specification.

2. Claim 34 is objected to for the use of the language "stringent conditions", which does not set forth the metes and bounds of the patent protection desired. A stringent condition could be very low to very high stringent condition.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

1. Claims 33-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying a compound that inhibits the mRNA expression of SEQ ID NO:1 *in vitro*, does not reasonably provide enablement for a method for identifying candidate therapeutic agents for the treatment of prostate cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 33-34 are drawn to a method for identifying candidate therapeutic agents for the treatment of prostate cancer, comprising determining the level of mRNA of an alpha-methylacyl-CoA racemase, which is SEQ ID NO:1 or 3 in the presence of a test compound, wherein the test compound is a candidate therapeutic agent for the treatment of prostate cancer if the mRNA level is less than a predetermined value.

Claims 33-34 encompass a method for identifying compounds that inhibit the mRNA expression of the racemase of SEQ ID NO:1 or 3, such as antisenses, wherein said compounds could be used for treating prostate cancer.

The specification discloses in example 1, table 1 on page 13, that the mRNAs of both the splice variants of alpha-methylacyl-CoA racemases, SV1 (SEQ ID NO:1, 3 and 4) and SV2 are overexpressed in prostate cancer tissues and prostate cancer metastasis. The specification further discloses that there are different variants of alpha-methylacyl-CoA racemases have different sequences, the structure of which is different from each other (p.11). The specification contemplates screening modulators of alpha-

methylacyl-CoA racemase expression, wherein the ability of the modulating agent can be confirmed in an animal with a disease, such as prostate cancer (p.45, last paragraph, bridging p.46). The specification further comtemplates making antisenses of alpha-methylacyl-CoA racemase, which includes ribozymes, for administering in a subject to inhibit transcription and translation of the target racemase (p.24-26).

One cannot extrapolate the teaching in the specification to the claims, because although SEQ ID NO:1 and 3 is overexpressed in prostate cancer and prostate cancer metastasis, one cannot predict that a screened sequence that inhibits the mRNA expression of SEQ ID NO:1 or 3 in a test sample *in vitro* could be used for treating prostate cancer for the following reasons:

1) There is no indication that SEQ ID NO:1 or 3 is responsible for prostate cancer development, and thus it is unpredictable that a screened sequence that inhibits the level of mRNA expression of SEQ ID NO:1 or 3 in a test sample *in vitro* would inhibit prostate cancer growth in *in vitro* and *in vivo* in a patient.

2) Further, one cannot extrapolate from *in vitro* inhibition of mRNA expression of SEQ ID NO:1 or 3 to *in vivo* killing prostate tumor cells by inhibition of mRNA expression of SEQ ID NO:1 or 3, because *in vitro* and *in vivo* conditions are different, and because the responses and characteristics of cultured cell lines generally differ significantly from the response and characteristics of a primary tumor. The enablement of the claimed invention appears to be based solely on in vitro data. The art however does not recognize a reliable correlation between in vitro assay data and effective in vivo efficacy for human tumor therapy. This is evidenced Kimmel et al.(J. Neurosurg,

66:161-171, 1987) who teach that in vitro assays cannot easily assess host-tumor and cell-cell interactions that may be important in the malignant state and cannot duplicate the complex conditions of in vivo therapy. Further, the responses and characteristics of cultured cell lines generally differ significantly from the response and characteristics of a primary tumor. Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded and that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the *bona fide* cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). Further, Embleton et al (Immunol Ser, 1984, 23:181-207) specifically teaches that in procedures for the diagnosis of osteogenic sarcoma, caution must be used when interpreting results obtained with monoclonal antibodies that had been raised to cultured cell lines and specifically teach that cultured tumor cells may not be antigenically typical of the tumor cell population from which they were derived and it is well established that new artifactural antigens can occur as a result of culture (see attached abstract). Hsu (in Tissue Culture Methods and Applications, Kruse and Patterson, Eds, 1973, Academic Press, NY, see abstract, p.764) specifically teaches that it is well known that cell cultures *in vitro* frequently change their chromosomal constitutions (see abstract). Mustafa O et al, 1996, Intl J Oncology, 8(5): 883-888, teach that prostate cells in late culture all show numerous changes in chromosome 5 in addition to some new markers. The evidence presented clearly demonstrates that in cell culture systems, in general,

and in cancer derived cell lines in particular, that artifactural chromosome constitutions and antigen expression are expected and must be taken into account when interpreting data received from cell line assays. Further, Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, petri dish cancer is a poor representation of malignancy, with characteristics profoundly different from the human disease Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary -type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate

the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interations. Thus, based on the cell culture data presented in the specification, it could not be predicted that, in the *in vivo* environment, the screened inhibitors of mRNA expression of SEQ ID NO:1 or 3 would be effective in treating prostate cancer.

3)) Further, one cannot extrapolate the teaching of the specification to the claims because it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Because of the known unpredictability of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the screened compounds that inhibit the mRNA expression of SEQ ID NO:1 or 3 *in vitro* would be useful for treating prostate cancer in a patient as claimed. Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense

mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). It is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that that the screened compounds that inhibit the mRNA expression of SEQ ID NO:1 or 3 *in vitro* would be useful for treating prostate cancer in a patient as claimed. In addition, Hartwell et al (Science, 1997, 278:1064-1068) teach that an effective chemotherapeutic must selectively kill tumor cells, that most anticancer drugs have been discovered by serendipity and that the molecular alterations that provide selective tumor cell killing are unknown and that even understanding the detailed molecular mechanism by which a drug acts often provides little insight into why the treated tumor cell dies (para bridging pages 1064-1065) and Jain (cited supra) specifically teaches that systemic treatment typically consists of chemotherapeutic drugs that are toxic to dividing cells (p. 58, col 2, para 2).

Further, a screened anti-tumor agent must accomplish several tasks to be effective. It must be delivered into the circulation that supplies the tumor and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. In addition the target cell must not have a alternate means of survival

despite action at the proper site for the drug. *In vitro* assays cannot duplicate the complex conditions of *in vivo* therapy. In the assays, the anti-tumor agent is in contact with cells during the entire exposure period. This is not the case *in vivo*, where exposure tat the target site may be delayed or inadequate. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieveing successful therapy. The anti-tumor agent may be inactivated *in vivo* before producing a sufficient effect, for example, by proteolytic degradation, immunological activation or due to an inherently short half life and the *in vitro* tests of record do not sufficiently duplicate the conditions which occur *in vivo*.. In addition, the antitumor agent may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the agent has no effect, circulation into the target area may be insufficient to carry the agent and a large enough local concentration may not be established.

4) In addition, as written, the claims encompass a method for screening antisenses that inhibit the mRNA expression of SEQ ID NO:1 or 2, wherein said antisenses could be used in gene therapy for treating prostate cancer. It is well known in the art however that gene therapy and *in vivo* therapy using antisense sequences is unpredictable. In the field of antisense technology, according to Gura (Science, 1995, 270:575-577), researchers have many reservations. Gura discloses that "the biggest concern is that antisense compounds simply don't work the way researchers once thought they did." Other drawbacks in animal studies include difficulty getting antisense oligonucleotides to target tissues and the existence of potentially toxic side effects such

as increased blood clotting and cardiovascular problems (page 575, col 1, para 2). Another problem stems from the fact that oligonucleotides used as controls produced the same biological effects in cell culture as did the antisense compounds (page 576, col 1, para 2 and 3). In addition, Gura reports problems with synthetic antisense oligonucleotides in that unwanted and sometimes lethal side effects occurred in animal experiments, and that they block cell migration and adhesion to underlying tissue in vitro (page 576, col 3, para 1 and 3). Thus a high degree of unpredictability is associated with the use of antisense constructs employed in methods of inhibiting expression of a particular protein in an animal model. Wang et al (PNAS, 1995, 92:3318-3322) specifically teach that therapeutic applications of antisense oligonucleotides are currently limited by their low physiological stability, slow cellular uptake and lack of tissue specificity (p. 3318, para 1). Problems with cellular uptake of antisense oligonucleotides are difficult to solve because endogenous uptake pathways generally have insufficient capacity to deliver the quantities of antisense oligonucleotides required to suppress gene expression and intracellular delivery and tissue specificity remain major obstacles to the implementation of antisense drugs in the treatment of human disorders (p. 3318, para bridging cols 1 and 2).

Moreover, the state of the art at the time of filing was that the combination of vector, promoter, protein, cell, target tissue, level of expression and route of administration required to target the tissue of interest and obtain a therapeutic effect using gene therapy was unpredictable. For example, Miller (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and

conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

In view of the above it would be undue experimentation for one of skill in the art to practice the claimed invention.

2. If Applicant could overcome the above 112, first paragraph rejection, claim 34 is still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying a compound that inhibits the mRNA expression of SEQ ID NO:1 or 3 *in vitro*, comprising exposing the test sample to a nucleic acid molecule which hybridizes to SEQ ID NO:1 or 3 under stringent conditions wherein the washes are at 0.2x SSC, 1% SDS at 65 ^{0}C, does not reasonably provide enablement for a method for identifying candidate therapeutic agents for the treatment of prostate cancer, comprising exposing the test sample to a nucleic acid molecule which hybridizes to SEQ ID NO:1 under "stringent conditions". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 34 is drawn to a method for identifying candidate therapeutic agents for the treatment of prostate cancer, comprising determining the level of mRNA of an alpha-methylacyl-CoA racemase, which is SEQ ID NO:1 or 3 in the presence of a test compound, wherein the test compound is a candidate therapeutic agent for the treatment of prostate cancer if the mRNA level is less than a predetermined value, wherein the step of measuring the level of expression of SEQ ID NO:1 or 3 comprises exposing the test sample to a nucleic acid molecule which hybridizes to SEQ ID NO:1 under "stringent conditions". .

The claim encompasses detecting polynucleotides comprising non-disclosed nucleic acid sequences attached to polynucleotides of SEQ ID NO:1 or 3. That is

polynucleotides that hybridize to said polynucleotides under stringent conditions. However, neither the specification nor the claims define what is meant by stringent conditions. As conventionally understood in the art and as taught by US Patent No. 5,912,143, hybridization is used to refer to any process by which a strand of nucleic acid binds with a complementary strand through base pairing (col 5, lines 3-5) and further teaches that numerous equivalent conditions may be employed to comprise either low or high stringency conditions and hybridization solutions may be varied to generate conditions of either low or high stringency (col 5, lines 57-67). The stringent conditions claimed read on both high and low stringency conditions. It is well known that the lower the stringency condition the more dissimilar the hybridizing molecule will be from the molecule to which it hybridizes. When given the broadest reasonable interpretation, the claims are clearly intended to encompass a variety of species including full-length cDNAs, genes and protein coding regions. Clearly, it would be expected that a substantial number of the hybridizing molecules encompassed by the claims **would not** share either structural or functional properties with the polynucleotides of SEQ ID NO:1 or 3.

In view of the above it would be undue experimentation for one of skill in the art to practice the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

MINH TAM DAVIS

May 16, 2003

SUSAN UNGAR, PH.D
PRIMARY EXAMINER